

General

Guideline Title

Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies.

Bibliographic Source(s)

Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ, on behalf of British Committee for Standards in Haematology. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012 Aug;158(3):323-35. [106 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Allford SL, Hunt BJ, Rose P, Machin SJ; Haemostasis and Thrombosis Task Force, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. Br J Haematol. 2003 Feb;120(4):556-73.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Diagnosis of Thrombocytopenic Purpura (TTP)

ADAMTS13 Assays

1. The diagnosis of TTP should be treated as a medical emergency (1A).
2. The initial diagnosis of TTP should be made on clinical history, examination and routine laboratory parameters of the patient, including blood film review (1A).
3. In view of the high risk of preventable, early deaths in TTP, treatment with plasma exchange (PEX) should be initiated as soon as possible, preferably within 4–8 h, regardless of the time of day at presentation, if a patient presents with a microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia in the absence of any other identifiable clinical cause (1B).
4. Serological tests for human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, autoantibody screen and when appropriate, a pregnancy test, should be performed at presentation (1A).
5. Pre-treatment samples should be obtained to measure ADAMTS13 activity levels and to detect anti-ADAMTS13 antibodies. Measurement of ADAMTS 13 antigen levels is also useful in congenital TTP cases (1B).

Subgroups of TTP

Congenital TTP

1. Congenital TTP should be considered in neonates presenting with severe jaundice. Presentation may also occur in childhood or as an adult (1A).
2. The diagnosis of congenital TTP should be considered in children and adults with unexplained thrombocytopenia (1B).
3. The diagnosis of congenital TTP is confirmed by ADAMTS13 activity <5%, absence of antibody and confirmation of homozygous or compound heterozygous defects of the ADAMTS13 gene (1A).

Drug-Associated TTP

1. Medications associated with precipitation of TTP include quinine and oestrogen-containing medications, which should be avoided to prevent relapse in patients with a previous episode of TTP (2C).
2. Women with previous TTP should be offered non-oestrogen containing contraception (1C).

Treatment of Acute TTP

Plasma Therapy

1. PEX should be started with 1.5 plasma volume (PV) exchanges, using solvent/detergent-treated (S/D) plasma in all age groups and reassessed daily (1B).
2. The volume of exchange can be reduced to 1.0 PV when the clinical condition and laboratory test results are stabilizing (2C).
3. Intensification in frequency and or volume of PEX procedures should be considered in life-threatening cases (2B).
4. Daily PEX should continue for a minimum of 2 d after platelet count has been $>150 \times 10^9/l$ and then stopped (2B).

Congenital TTP

1. S/D plasma infusion or intermediate purity Factor VIII (e.g., BPL 8Y) should be used to treat congenital TTP (1C).
2. Treatment regimens for congenital TTP should be individualized according to the patient's phenotype (1A).

Treatment of TTP in Pregnancy

1. If a thrombotic microangiopathy (TMA) cannot be fully explained by a non-TTP pregnancy-related TMA, then the diagnosis of TTP must be considered and PEX should be started (2B).
2. Mothers with congenital TTP should attend a specialist centre and receive ADAMTS13 supplementation regularly throughout pregnancy and the post-partum period (1A).
3. Close liaison with an obstetrician with a special interest in feto-maternal medicine is required in mothers with TTP (1A).
4. In mothers with acquired TTP, ADAMTS13 activity should be monitored throughout pregnancy to help predict the need for adjuvant therapy and outcome (1B).
5. Pre-conceptual counselling is advised for subsequent pregnancies and women of child bearing age should be counselled about potential risks of pregnancy and combined oral contraceptive pill (COCP) (2B).

HIV-related TTP

1. If a patient with TTP is found to have HIV infection then viral load should be measured and an HIV physician should be closely involved in management (1A).
2. TTP should be considered in an HIV-positive individual with a MAHA and thrombocytopenia (1A).
3. PEX in conjunction with highly active antiretroviral therapy (HAART) (triple or quadruple therapy) should be started as soon as the diagnosis of HIV-associated TTP is made (1B).
4. HAART should be given immediately after PEX therapy to maximize time for absorption (1A).
5. HAART should be continued after remission to prevent further relapse (1B).
6. In resistant HIV-related TTP, rituximab could be considered (2B).

Malignancy-Associated Thrombotic Microangiopathy

1. PEX is not indicated in the management of malignancy and bone marrow transplant-associated TMA (1A).
2. In cancer associated TMA, further treatment for the underlying cancer should be considered (1A).

Further Treatments in Acquired TTP

Corticosteroids

1. Intravenous daily methylprednisolone (e.g., 1 g/d for three consecutive days – adult dose) or high dose oral prednisolone (e.g., 1 mg/kg/d) should be considered (1B).

Rituximab

1. In acute idiopathic TTP with neurological/cardiac pathology, which are associated with a high mortality, rituximab should be considered on admission, in conjunction with PEX and steroids (1B).
2. Patients with refractory or relapsing immune-mediated TTP should be offered rituximab (1B).

Ciclosporin A (CSA) and Tacrolimus

1. CSA may be considered as second line therapy in patients with acute or chronic relapsing acquired TTP (1C).

Splenectomy

1. Splenectomy may rarely be considered in the non-acute period of immune-mediated TTP but has limited proven benefit (2C).

Antiplatelet Agents

1. The clinical efficacy of antiplatelet agents in TTP is unproven but they are relatively safe (1B).
2. Low dose aspirin (75 mg once per day [OD]) may be given during platelet recovery (platelet count $>50 \times 10^9/l$) (2B).

Supportive Therapy

1. Red cell transfusion should be administered according to clinical need especially if there is cardiac involvement (1A).
2. Folate supplementation is required during active haemolysis (1A).
3. Platelet transfusions are contraindicated in TTP unless there is life-threatening haemorrhage (1A).
4. Thromboprophylaxis with low molecular weight heparin (LMWH) is recommended once platelet count has reached $>50 \times 10^9/l$ (1B).

Refractory TTP

Increased frequency of PEX and addition of rituximab can be considered in refractory TTP (1B).

Relapse

1. Increased PEX and/or rituximab therapy are the agents of choice in relapsing disease (1B).
2. Patients should be counselled about symptoms, signs and risk of relapse before discharge with verbal and written information (1A).
3. In patients with a documented reduction of ADAMTS 13 activity to $<5\%$, elective therapy with rituximab can be considered (1B).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is uncertain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

An algorithm for the summary of treatment protocol for acute thrombotic thrombocytopenic purpura (TTP) is provided in the original guideline document.

Scope

Disease/Condition(s)

- Thrombotic thrombocytopenic purpura (TTP)
- Other thrombotic microangiopathies defined by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and small vessel thrombosis

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Hematology

Internal Medicine

Obstetrics and Gynecology

Pediatrics

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals with clear, up-to-date, and practical guidance on the management of thrombotic thrombocytopenic purpura

(TTP) and related thrombotic microangiopathies (TMA), defined by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and small vessel thrombosis

Target Population

People in the United Kingdom with suspected or confirmed thrombotic thrombocytopenic purpura (TTP) and related thrombotic microangiopathies

Interventions and Practices Considered

Diagnosis/Evaluation

1. Clinical history, examination and routine laboratory parameters, including blood film review
2. Serological tests for human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, autoantibody screen and, when appropriate, a pregnancy test
3. Measurement of ADAMTS13 activity levels and to detect anti-ADAMTS13 antibodies
4. Measurement of ADAMTS 13 antigen levels in cases of congenital thrombotic thrombocytopenic purpura (TTP)

Treatment/Management

1. Plasma exchange (PEX) using solvent/detergent-treated (S/D) plasma
2. Intensification in frequency and or volume of PEX procedures in life-threatening cases
3. Intermediate purity Factor VIII (e.g., BPL 8Y) infusion
4. Avoiding quinine and oestrogen-containing medications in drug-associated TTP
5. Treatment regimens for congenital TTP individualized according to the patient's phenotype
6. Treatment considerations for TTP in pregnancy
7. Treatment considerations for TTP in patients with human immunodeficiency virus (HIV) infection
 - PEX in conjunction with highly active antiretroviral therapy (HAART) (triple or quadruple therapy)
 - Rituximab in resistant HIV-related TTP
8. Treatment considerations for malignancy-associated thrombotic microangiopathy (PEX should not be used)
9. Additional treatment
 - Intravenous methylprednisolone or high-dose oral prednisolone
 - Rituximab
 - Ciclosporin A and tacrolimus
 - Splenectomy
 - Anti-platelet agents
10. Supportive treatment
 - Red cell transfusion
 - Folate supplementation
 - Thromboprophylaxis with low molecular weight heparin (LMWH)
11. Increased frequency of PEX and addition of rituximab in refractory and relapsing TTP

Major Outcomes Considered

- Prognostic value of diagnostic tests
- Remission rate
- Relapse rate
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

METHODS USED TO COLLECT/SELECT THE EVIDENCE

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

MEDLINE and EMBASE were searched systematically for publications in English, using the keywords: thrombotic thrombocytopenia purpura (TTP), ADAMTS13, plasma exchange (PEX) and relevant key words related to the subsections of this guideline. The period of literature included was up until October/November 2011.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used to quote levels and grades of evidence, details of which can be found at <http://www.bcsghguidelines.com> .

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline group was selected to be representative of UK-based medical experts. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of British haematologists, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology Committee and comments incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate diagnosis and management of thrombotic thrombocytopenic purpura (TTP) and related thrombotic microangiopathies
- Improved survival rates

Potential Harms

- The UK Department of Health recommends the use of solvent/detergent-treated (S/D) plasma in thrombotic thrombocytopenic purpura (TTP) patients to reduce the risk of transfusion-transmitted infection and adverse immune responses.
- In the UK, single donor methylene blue-treated fresh frozen plasma (MB-FFP) is the recommended plasma for use in all indications in those born after 1st January 1996 to minimize the risk of prion transmission. However MB-FFP has been associated with increased numbers of plasma exchanges and longer hospital stay in TTP.

- Plasma-related adverse events, such as allergic reactions, anaphylaxis and central venous catheter thrombosis, appeared to be more frequent prior to the use of S/D plasma.
- Higher dose pulsed steroids usually have minimal side effects.
- The mortality of open splenectomy in acute TTP was reported to be approximately 40%.

Contraindications

Contraindications

Due to the risk of precipitating further thrombotic events, platelet transfusions are contraindicated unless there is life-threatening haemorrhage.

Qualifying Statements

Qualifying Statements

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ, on behalf of British Committee for Standards in Haematology. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012 Aug;158(3):323-35. [106 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2003 Feb (revised 2012 Aug)

Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

Haemostasis and Thrombosis Task Force

Composition of Group That Authored the Guideline

Authors: Marie Scully, Department of Haematology, UCLH, London; Beverley J. Hunt, Department of Haematology, King's College and Guys & St Thomas' NHS Trust, London; Sylvia Benjamin, Department of Haematology, NBSBT and Oxford University Hospitals (OUH) Trust, UK; Ri Liesner, Department of Haematology, GOSH, London; Peter Rose, Department of Haematology, University Hospitals Coventry & Warwickshire NHS trust, Coventry, UK; Flora Peyvandi, Department of Haematology, IRCCS Maggiore Hospital Ca' Granda Foundation, University of Milan, Milan, Italy; Betty Cheung, Department of Haematology, Queen Elizabeth Hospital, SLHT, London; Samuel J. Machin, Department of Haematology, UCL, London, UK

Financial Disclosures/Conflicts of Interest

The Haemostasis Research unit, UCL has received an unrestricted educational grant from Octapharma, UK.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Allford SL, Hunt BJ, Rose P, Machin SJ; Haemostasis and Thrombosis Task Force, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. Br J Haematol. 2003 Feb;120(4):556-73.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the [British Committee for Standards in Haematology Web site](#)

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 27, 2012. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab). This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

Copyright Statement

This NGC summary is based on the original guideline, which is copyrighted by the British Committee for Standards in Haematology. For more information, contact the BCSH Secretary, 100 White Lion Street, London, UK, N1 9PF; Email: bcsh@b-s-h.org.uk.

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouse[®] (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at <http://www.guideline.gov/about/inclusion-criteria.aspx>.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.